TSUMURA & CO.
12-7, Nibancho, Chiyoda-ku, Tokyo 102-8422, Japan



October 3, 2000

Tsumura & Co.
12-7 Nibancho
Chiyoda-ku, Tokyo 102-8422
Japan

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Subject: Docket 00D-1392, Draft Guidance for Industry on Botanical Drug Products

To whom it may concern:

Tsumura & Company is pleased to have the opportunity to provide comments on Draft Guidance for Industry: Botanical Drug Products, Docket 00D-1392 (published in Federal Register, August 11, 2000).

CMC:

Regarding section IX.B., in order to ensure pharmaceutical uniformity of botanical drug products, we believe it is necessary to conduct additional critical tests, namely disintegration studies or dissolution studies tests, and specify acceptable standards.

Section IX.B.2.i states that the FDA intends to conduct inspection of manufacturing and testing facilities for the drug substance and drug product. Will FDA accept the results of inspection conducted by another country as a substitute for FDA conducting the inspection in that country, if the botanical drug product is manufactured and tested in compliance with GMP and approved as a drug product in that country?

Bioavailability:

Regarding section VII.D., in determining the bioavailability, we at Tsumura & Co., intend to conduct measurements of ingredients if the measurements can rationally be used to support clinical efficacies. We also believe that measurement of components that do not support clinical efficacies cannot be used in the design and interpretation of drug administration and thus is unnecessary. We believe that consultations with the FDA will clarify the basis for this position.

Clinical Considerations

We understand the importance of placebo-controlled randomized double blind studies as described in section VI.B.5. In contrast to new drugs, treatments using botanical drug products are often holistic, and for this reason, components contained in placebo may affect endpoints used in clinical evaluation. For example, in preparing a placebo for the botanical drug product, taste components or bitterness may need to be added to the placebo to preserve the identical appearance of the drug and the placebo. We have previously experienced difficulty in completing a clinical trial because of the effect of such components on the endpoints. Therefore, rather than requiring a specified inactive placebo, we believe that clinical studies employ a design suitable for the circumstances.

Marketing:

Regarding section III.A., there exists a tradition of using Kampo herbal drug products in Japan as approved prescription drugs, but there is no use experience of such products in the United States as a drug product. Thus, we have interpreted this situation to mean that marketing exclusivity will be for 5 years as a new chemical entity, and believe that this interpretation should be explicitly specified.

Relating to section III.A., once the period of marketing exclusivity has passed, a competing firm could plan to market a generic product by obtaining an ANDA. But we

believe that because of the special characteristics of botanical drug products, it is actually impossible to manufacture drugs which are equivalent to innovator drugs in quality. We believe that this interpretation may also be used to allow protection of the innovator drug manufacturer along with the period of exclusivity.

In addition, while the developmental steps to Phase II may be abbreviated, it is still required that testing required of any new drug be conducted in Phase III studies. Even if a botanical drug product is developed despite high developmental costs, a less expensive DS product may be marketed soon and occupy the market. It is easily considered that a manufacturer will be discouraged from developing botanical drugs instead of DS products. We strongly hope FDA should solve this serious problem.

We trust that botanical drug products with superior utility and quality approved based on final Guidance will lead to improved health for all Americans. We shall be happy to make the expertise of our company available to you in the preparation of the final Guidance.

Best wishes,

Hiro Sasaki

Hiromi Sasaki, Ph.D.
Director of Business and Product Development
International Division

DHL WORLDWIDE EXPRESS

**Air Cargo Receipt**
(貨物受取書)
(Non-negotiable)

580861 80A

**JP** 2960474716

Quote this shipment number in an enquiry

ORIGIN: TYO

DESTINATION: GAI

## 1 From (発送人)

Account no. (顧客番号): 580861 80

Sender's name (担当者名): H. Kodaira

Sender's reference *first twelve characters will be shown on invoice*:

Company name (会社名): TSUMURA & CO., LTD.

Address (住所):
12-7, NIBAN-CHO
CHIYODA-KU, TOKYO 102-8422
JAPAN

Postcode (郵便番号):

Phone (電話番号): 03-3221-0001

着払い運賃に関し受取人が支払を拒否した場合は、発送人が支払う事を保証致します。

## 2 To (受取人)

Company name (会社名):
Dockets Management Branch
Food and Drug Administration (HFA-305)

Delivery address (住所):
5630 Fishers Lane, Rm. 1061
Rockville,

DHL CANNOT DELIVER TO A PO BOX
私書箱への配達は出来ませんのでご注意ください。

(US)

Postcode (郵便番号): MD 20852

Country (国名): USA

Contact person (担当者名): Dr. Yuan-Yuan Chiu

Phone/Fax (電話／ファックス番号): TEL 301-827-5918

## 3 Shipment details

- [X] DOX
- [ ] WPX
- [ ] EDX
- [ ] DPX
- [ ] OTHERS.....

**Shipment insurance** (荷主保険)
- [ ] YES [redacted]

- [X] Sender
- [ ] Cash/Cheque/Credit Card

*For approved customers only*
- [ ] External Billing Agreement
- [ ] Transport Collect

**Full description of contents** (内容)

LETTER

Declared value *give currency*:

Sender's VAT/GST no.:

Harmonised commodity code *if applies*:

Receiver's VAT/GST no. or EIN/SSN:

Type of export: [ ] PERMANENT [ ] REPAIR/RETURN [ ] TEMPORARY

Destination duties/taxes *if left blank receiver pays duties/taxes* (輸入関税請求先)
- [ ] Receiver (受取人)
- [ ] Sender (発送人)
- [ ] Other.....
*Specify destination approved account number*

## 4 Size and weight

| No. of pieces (個数) | Weight (重量) |
|---|---|
| 1 | 0.5 kg |

Dimensions *cm L x W x H* (サイズ)

x x

VOLUMETRIC/CHARGED WEIGHT: . kg

| CODES | CHARGES |
|---|---|
| | Services |
| | Special |
| | Insurance |
| | Other/VAT |

CURRENCY CODE | TOTAL

TRANSPORT COLLECT STICKER No.

DATE: 10/5

PICKED UP BY

Route No.: AK34

Time

Date

Consignee copy

MP 03/99 C